Synthesis of carbamate derivatives of dibromodibenzo[*d,g*][1,3,6,2] dioxathiaphosphocin 6-oxides

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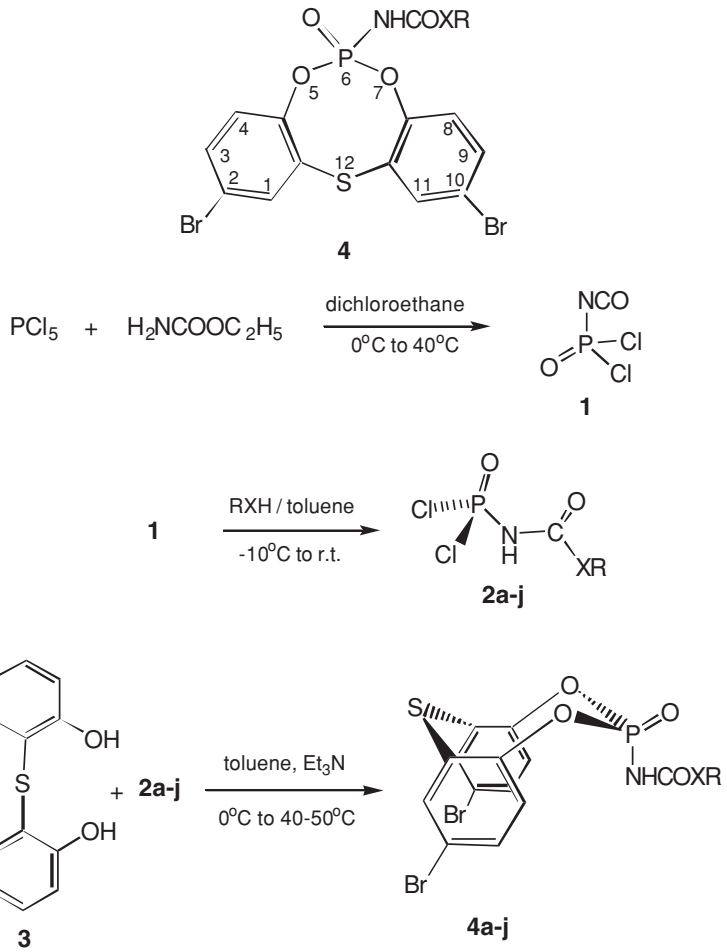
6-Alkylcarbamato-2,10-dibromodibenzo[*d,g*][1,3,6,2]dioxathiaphosphocin 6-oxides were prepared by cyclisation of 5,5′-dibromo-2,2′-dihydroxydiphenyl sulfide with dichlorophosphinyl carbamates/thiocarbamates, obtained by the addition of alcohols/thiols to dichloroisocyanatophosphine oxide, and characterised by IR, ^{1}H, ^{13}C, ^{31}P NMR and mass spectral studies.

Keywords: diaryl sulfides, phosphoramidates, phosphorus heterocycles, carbamates

Some heterocyclic phosphorus esters have been reported[1-3] to possess insecticidal and bactericidal properties. Industrially, they have been found useful as lubricating oil additives, antioxidants and polymer stabilisers.[4] Phosphorus carbamates are an important class of antitumor agents and pesticides.[5,6] In view of the wide applications of organophosphorus carbamates, we prepared the title compounds **4a–j** and characterised them by elemental and spectral analysis.

6-Alkylcarbamato-2,10-dibromodibenzo[*d,g*][1,3,6,2]dioxathiaphosphocin 6-oxides (**4a–j**) were synthesised in a two step process. (Scheme 1) In the first step, the addition of dichloroisocyanatophosphine oxide (**1**) with various alcohols and thiols at –10 °C under anhydrous conditions in dry toluene afforded the corresponding dichlorophosphinyl carbamates and thiocarbamates (**2a–j**). Interestingly, all the primary and secondary alcohols reacted readily with dichloroisocyanatophosphine oxide to give the respective carbamates (**2a–i**), but tertiary alcohols did not react under the same conditions, obviously due to steric factors. In the second step, compounds **2a–j** were cyclised *in situ* with 5,5′-dibromo-2,2′-dihydroxydiphenyl sulfide[7] (**3**) in the presence of triethylamine at 40–50 °C to give the compounds **4a–j**. Since all the products were solvent- and heat-sensitive, they could not be purified by recrystallisation. However, they were obtained in pure form by column chromatography on silica gel with ethyl acetate-hexane as eluant.



Scheme 1

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Compound	XR	Compound	XR
4a	OCH_3	**4f**	$OCH_2CH{=}CH_2$
4b	OCH_2CH_3	**4g**	$OCH_2C{\equiv}CH$
4c	OCH_2CH_2Cl	**4h**	$OCH_2C_6H_5$
4d	$OCH_2CH_2CH_3$	**4i**	$OCH_2CH_2C_6H_5$
4e	$OCH(CH_3)_2$	**4j**	$SCH_2CH_2CH_3$

Compounds **4a–j** exhibited characteristic IR absorptions[8-10] in the region 3072–3179 cm^{-1} (NH), 1726-1776 cm^{-1} (C=O), and 1207–1217 cm^{-1} (P=O). Only three sets of signals for the six protons of the dibromodibenzodioxathiaphosphocin moiety were observed.[11] This showed the symmetrical disposition of the two substituted benzene rings in the dibenzodioxathiaphosphocin moiety.[12] The doublet of doublets in the region δ 7.12–7.17 (J = 8.6,1.2 Hz) was assigned to H(4) and H(8). Another doublet of doublets at δ 7.46–7.51 (J = 8.6,1.2 Hz) was attributed to H(3) and H(9). H(1) and H(11) resonated as a doublet at δ 7.73–7.83 (J = 1.6-2.4 Hz). P-NH proton signals were not observed.[13] The signals for the protons of the carbamate function appeared slightly downfield when compared to those of corresponding protons in the free alcohols/ thiols.[14]

The ^{13}C NMR chemical shifts were interpreted based on comparison with carbon chemical shifts of **3** and related system.[11,15] The carbon chemical shifts of the carbamate function appeared downfield in all compounds when compared with the signals of the corresponding carbon chemical shifts in the respective free alcohols/ thiols.[14] The remaining carbons of the carbamate function resonated in the expected regions.

The ^{31}P NMR signals[15] for the carbamate compounds (**4a–j**) appeared at δ –6.25 to –15.88, whereas the thiocarbamate compound **4j** it appeared at the upfield at δ –19.60. This may be attributed to the difference in the electrochemical natures of oxygen and sulfur.

Fab mass spectra of **4b** and **4c** showed protonated molecular ion peaks at 508 (16.0) and 522 (52.7) with isotopic peak ions 512 (MH+4, 61.4), 510 (MH+2, 100) and 526 (MH+4, 45.1), 524 (MH+2, 100) respectively. Compound **4b** showed $[M\text{-}C_2H_5O_2]^+$, $[M\text{-}NCOOCH_2CH_3]^+$, $[M\text{-}SH_6Br]^+$, $[M\text{-}C_3H_8O_5NSP]^+$ and $[M\text{-}CH_2H_5O_2, Br_2]^+$ ion peaks at *m/z*(%) 447 (6.2), 391(66.6), 307 (27.3), 289 (18.9) respectively. In **4e** $[M\text{-}C(CH_3)_2]^+$, $[M\text{-}C_4H_5O_2]^+$ and $[M\text{-}NCOOCH(CH_3)_2]^+$, ion peaks at *m/z*(%) 481 (19.0), 438 (10.6), 421 (10.6), 391 (38.2).

FAB mass spectra of **4b** and **4e** showed protonated molecular ion peaks as the most abundant ion peaks at *m/z* 510 $(M+1,100)^+$ and 524 $(M+1,100)^+$ respectively. Compound **4b** showed $[M\text{-}C_2H_6O_2]^+$, $[M\text{-}NHCOOCH_2CH_3]^+$, $[M\text{-}C_3H_5O_4N]^+$, $[M\text{-}C_2H_6O_2\text{-}Br_2]^+$ and $[M\text{-}CH_3CH_2COON, O_2]^+$ ion peaks at *m/z* (%), 447 (6.2), 421(4.5), 391 (66.6), 307 (27.3), 289 (18.7) respectively. In **4e**, $[M\text{-}CH(CH_3)_2]^+$, $[M\text{-}CO_2\text{-}CH_3CH{=}CH_2]^+$, $[M\text{-}NHCOOCH(CH_3)_2]^+$ and $[M\text{-}NHCOOCH\ (CH_3)_2, O_2]^+$ peaks were observed at *m/z* (%), 481 (49), 438 (10.6), 421 (6.3), 391 (38.2).

Experimental

Melting points were determined in open capillary tubes. Elemental analyses were performed at the Central Drug Research Institute, Lucknow, India. IR spectra were recorded as KBr pellets on a Perkin-Elmer 1430 unit. All NMR spectra were recorded on an AMX-400 MHz, spectrometer, operating at 400 MHz for ^1H, 100 MHz for ^{13}C and 161.9 MHz for ^{31}P. Compounds were dissolved in $CDCl_3$ and the chemical shifts were referenced to TMS (^1H, ^{13}C) and 85% H_3PO_4 (^{31}P). FAB mass spectra were recorded on a JEOL D-300 instrument at 70ev. Chromatographic purification was carried out on 60-120 mesh silica gel, using the eluents as specified for the individual preparations.

2,10-Dibromo-6-ethylcarbamatodibenzo[d,g][1,3,6,2]dioxathiaphosphocin 6-oxide (**4b**): A solution of ethanol (0.46 g 0.01 mol) in 20 ml of dry toluene was added dropwise to a cold solution (–10 °C) of dichloroisocyanatophosphine oxide[1] **1** (1.60 g 0.01 mol) in 20 ml of dry toluene. After the addition, the temperature of the reaction mixture was allowed to rise slowly to room temperature and stirring was continued for a further 2 h. The reaction mixture was added dropwise into a cold solution (0 °C) of **3** (3.76 g, 0.01 mol) and triethylamine (2.02 g 0.02 mol) in 30 ml of dry toluene. After completion of the addition, the temperature of the reaction mixture was allowed to rise slowly to 40–45 °C and stirring was continued for an additional 5 h. The precipitated triethylamine hydrochloride was filtered off and the solvent from the filtrate was evaporated under reduced pressure. The residue was washed with water followed by chilled 2-propanol. Column chromatography using ethyl acetate and hexane in 1:2 ratio as eluent afforded the pure compound **4b**. Similar procedures, employing the required alcohols or thiols, afforded the analogous compounds **4** as indicated.

2,10-Dibromo-6-(methylcarbamato)dibenzo[d,g][1,3,6,2]dioxathiaphosphocin 6-oxide (**4a**): Yield 54%, m.p.: 160–162 °C. IR (KBr): ν_{max}1214 (P=O), 1752 (C=O), 3140 cm^{-1} (NH). ^1H NMR: δ 7.80 (d, J = 1.6 Hz, H-1, 11), 7.48 (dd, J = 8.6, 1.2 Hz, H-3, 9), 7.18 (dd, J = 8.6, 1.2Hz, H-4, 8), 3.78 (s, 3H, OCH_3). ^{13}C NMR: δ 142.5 (s, 2C, C-1, 11), 139.2, (s, 2C, C-2, 10), 131.3 (s, 2C, C-3, 9), 123.5 (s, 2C, C-4, 8),153.2 (d, J = 8.0 Hz, 2C, C-4a, 7a), 129.0 (s, 2C, C-11a, 12a), 152.4(s, C=O), 58.0 (s, OCH_3). ^{31}PNMR: –8.25. Anal. Calcd. for $C_{14}H_{10}Br_2NO_5PS$ (495.08): C, 33.96; H, 2.03; N, 2.82. Found C, 33.79; H, 2.01; N, 2 80 %.

2,10-Dibromo-6-(ethylcarbamato)dibenzo[d,g][1,3,6,2]dioxathiaphosphocin 6-oxide (**4b**): Yield 56%, m.p.: 172–173 °C. IR (KBr): ν_{max} 1212 (P=O), 1745 (C=O), 3156 cm^{-1} (NH). ^1H NMR: δ 7.81 (d, J = 2.3Hz, H1, 11), 7.47 (dd, J = 8.6, 1.4 Hz, H-3, 9), 7.11 (dd, J = 8.6, 1.3 Hz, H-4, 8), 4.20 (m, 2H, OCH_2), 1.31 (t, 3H, CH_3). ^{13}C NMR: δ 138.1 (s, 2C, C-1, 11), 134.4 (s, 2C, C-2, 10), 126.1 (s, 2C, C-3, 9), 119.0 (s, 2C, C-4, 8), 152.0 (d, J = 9.3 Hz, C-4a, 7a), 123.0 (s, 2C, C-11a, 12a) 152.7 (C=O), 63.1 (OCH_2), 14.3 (CH_3). ^{31}P NMR: –12.17. FAB MS: 510 (M+1, 100), 447 (6.2), 421 (14.5), 391 (67), 371 (4.1), 367 (27), 289 (19), 279 (14.5), 154 (27). Anal. Calcd for $C_{15}H_{12}Br_2NO_5PS$ (509.11): C, 35.38; H, 2.37; N, 2.75. Found C, 35.94; H, 3.09; N, 3.01 %.

Change in mass data as 512 (MH+4, 61.4), 510 (MH+2, 100), 508 (16.0).

2,10-Dibromo-6-(chloroethylcarbamato)dibenzo[d,g][1,3,6,2]dioxathiaphosphocin 6-oxide (**4c**): Yield 58%, m.p. 152–153 °C. IR (KBr): ν_{max} 1207 (P=O), 1770 (C=O), 3076 cm^{-1} (NH). ^1H NMR: δ 7.83 (d, J = 2.3 Hz, H-1, 11), 7.51 (dd, J = 8.6, 1.0 Hz, H-3, 9), 7.17 (dd, J = 8.6,1.0 Hz, H-4, 8), 4.57 (t, 2H, OCH_2), 4.16 (t, 2H, CH_2Cl). ^{13}C NMR: δ 138.4 (s, 2C, C-1, 11), 133.8 (s, 2C, C-2, 10). 129.8 (s, 2C, C-3, 9), 117.0 (C-4, 8), 153.5 (d, J = 9.3 Hz, C-4a, 7a), 123.0 (s, 2C, C-11a, 12a), 151.8 (C=O), 68.4 (s, OCH_2), 21.9 (CH_2Cl). ^{31}P NMR: –15.88. Anal. Calcd for $C_{15}H_{11}Br_2ClNO_5PS$ (543.55): C, 33.14; H, 2.03; N, 2.57. Found C, 33.00; H, 2.01; N, 2.53 %.

Change in mass data as 526 (MH+4, 45.1), 524 (MH+2, 100), 522 (52.7).

2,10-Dibromo-6-(n-propylcarbamato)dibenzo[d,g][1,3,6,2]dioxathiaphosphocin 6-oxide (**4d**): Yield 56%, m.p.: 162–163 °C. IR (KBr): ν_{max} 1210 (P=O), 1776 (C=O), 3104 cm^{-1} (NH). ^1H NMR: δ 7.80 (d, J = 2.2Hz, H-1, 11), 7.48 (dd, J = 8.4, 1.2 Hz, H-2, 10), 7.16 (d, d. J = 8.4, 1.2 Hz, H-3, 9), 4.32 (t, 2H, OCH_2), 2.01 (m, 2H, CH_2), 1.20 (t, 3H, CH_3). ^{31}P NMR: –13.10. Anal. Calcd for $C_{16}H_{14}Br_2NO_5PS$ (523.13): C, 36.73; H, 2.69; N, 2.67. Found: C, 36.61; H, 2.67; N, 2.64 %.

2,10-Dibromo-6-(isopropylcarbamato)dibenzo[d,g][1,3,6,2]dioxathiaphosphocin 6-oxide (**4e**): Yield 51%, m.p.:167–168 °C. IR (KBr): ν_{max} 1216 (P=O), 1740 (C=O), 3179 cm^{-1} (NH). ^1H NMR: δ 7.82 (d, J = 2.4 Hz, H-1, 11), 7.49 (dd, J = 8.6, 1.4 Hz, H-3, 9), 7.14 (dd, J = 8.6, 1.3 Hz, H-4, 8), 5.05 (m, 1H, OCH), 1.33 (d, 6H, CH_3). ^{13}C NMR: δ 138.1 (s, 2C, C-1, 11), 134.4 (s, 2C, C-2, 10). 126.2 (s, 2C, C-3, 9), 119.0 (C-4, 8), 152.0 (d, J = 9.3Hz, C-4a, 7a), 123.1 (s, 2C, C-11a, 12a), 152.5 (d, J = 5.6 Hz, C=O), 71.3 (s, OCH), 21.9 (CH_3). ^{31}P NMR: –14.40. FAB MS: 524 (M+1 100), 481 (49), 438 (10.6), 421 (6.3), 391 (38), 307 (12.7), 289 (10.6), 232 (4.2), 154 (25.5), 136 (17.8). Anal. Calcd for $C_{16}H_{14}Br_2NO_5PS$ (523.13): C 36.73; H, 2.69; N, 2.67. Found: C, 36.58; H, 2.68; N, 2.63 %.

6-(Allylcarbamato)-2,10-dibromodibenzo[d,g][1,3,6,2]dioxathiaphosphocin 6-oxide (**4f**): Yield 50%, m.p.: 192–193 °C. IR (KBr): ν_{max} 1213 (P=O), 1738 (C=O), 3118 cm^{-1} (NH). ^1H NMR: δ 7.79 (d, J = 2.0 Hz, H-1, 11), 7.49 (dd, J = 8.4, 1.0 Hz, H-3, 9), 7.12 (dd, J = 8.4, 1.0 Hz, H-4, 8) 4.67 (d, 2H, OCH_2), 5.33 (m, 1H, CH), 5.18 (d, J_{trans} = 15.6Hz, CH_2), 5.16 (d, J_{cis} = 10.0Hz, CH_2). ^{13}C NMR: δ 138.1 (s, 2S, C-1, 11), 134.4 (s, 2C, C-2, 10), 126.0 (s, 2C, C-3, 9), 119.0 (s, 2C, C-4, 8), 152.0 (d, J = 8.9Hz, C-4a, 7a), 123.8 (s, 2C, C-11a, 12a), 152.5 (C=O) 67.8 (s, 1C, OCH_2) 118.6 (s, 1C, CH), 112.2

(s, 1C, CH_2). ^{31}P NMR: –19.60. Anal. Calcd for $C_{16}H_{12}Br_2NO_5PS$ (521.13): C, 36.88; H, 2.32; N, 2.69. Found: C, 36.68; H, 2.29; N, 2.57 %.

2,10-Dibromo-6-(propargylcarbamato)dibenzo[d,g][1,3,6,2] dioxathiaphosphocin 6-oxide (**4g**): Yield 52%, m.p.: 182–183 °C. IR (KBr): ν_{max} 1213 (P=O), 1748 (C=O), 3149 (NH), 2130 (C≡C), 3289 cm^{-1}. ^1H NMR: δ 7.82 (d, *J* = 2.2Hz, H-1, 11), 7.46 (dd, *J* = 8.6, 1.0 Hz, H-3, 9), 7.13 (dd, *J* = 8.6, 1.0 Hz, H-4, 8), 4.60 (m, 2H, OCH_2), 3.37 (m, IH, CH). ^{31}P NMR: –11.82. Anal. Calcd for $C_{16}H_{10}Br_2NO_5PS$ (519.12): C, 37.02; H, 1.94; N, 2.70. Found: C, 36.76, H, 1.88; N, 2.62 %.

6-(Benzylcarbamato)-2,10-dibromodibenzo[d,g][1,3,6,2]dioxathiaphosphocin 6-oxide (**4h**): Yield 54%, m.p.: 186–188 °C. IR (KBr): ν_{max} 1214 (P=O), 1726 (C=O), 3072 cm^{-1} (NH). ^1H NMR: δ 7.75 (d, *J* = 2.2Hz, H-1, 11), 7.30 (dd, *J* = 8.6, 1.0 Hz, H-3, 9), 7.15 (dd, *J* = 8.6, 1.0 Hz, H-4, 8), 4.60 (m, 2H, CH_2), 6.60–7.05 (m, 5H, Ar-H). ^{13}C NMR: δ 138.0 (s, 2C, C-1, 11),134.9 (s, 2C, C-2, 10). 129.0 (s, 2C, C-3, 9), 119.0 (C-4, 8), 152.0 (d, *J* = 8.9Hz, C-4a, 7a), 123.8 (s, 2C, C-11a, 12a) 153.0 (d, *J* = 5.3Hz, C=O), 68.6 (s, C-2′), 134.7 (C-3′),128.6 (C-4′),127.8 (C-5′),126.0 (C-6′),127.8 (C-7′),128.8 (C-8′). ^{31}P NMR: –11.82. Anal. Calcd for $C_{20}H_{14}Br_2NO_5PS$ (571.18): C, 42.06; H, 2.47; N 2.45. Found: C, 41.83; H, 2.44; N, 2.43 %.

2,10-Dibromo-6-(phenylethylcarbamato)dibenzo[d,g][1,3,6,2] dioxathiaphosphocin 6-oxide (**4i**): Yield 58%, m.p.: 180–182 °C. IR (KBr): ν_{max} 1267 (P=O), 1734 (C=O), 3072 cm^{-1} (NH). ^1H NMR: δ 7.73 (d, *J* = 1.8 Hz, H-1, 11), 7.47 (dd, *J* = 8.6, 1.2 Hz, H-3, 9), 7.15 (dd, *J* = 8.6, 1.2 Hz, H-4, 8), 4.24 (m, 2H, CH_2), 2.82 (m, 2H, CH_2), 6.7–7.10 (m, 5H, Ar-H). ^{31}P NMR: –11.11. Anal. Calcd for $C_{21}H_{16}O_5Br_2PSN$ (585.42): C, 43.10; H, 2.75; N 2.39. Found: C, 43.03; H, 2.69; N, 2.32 %.

2,10-dibromo-6-(propylthiocarbamato)dibenzo[d,g][1,3,6,2]dioxathiaphosphocin 6-oxide (**4j**): Yield 60%, m.p.: 190–192 °C. IR (KBr): ν_{max} 1228 (P=O), 1726 (C=O), 3172 cm^{-1} (NH). ^1H NMR: δ 7.68 (d, *J* = 1.6 Hz, H-1, 11), 7.36 (dd, *J* = 8.6, 1.2 Hz, H-3, 9), 7.14 (dd, *J* = 8.6, 1.2 Hz, H-4, 8), 2.62 (m, 2H, CH_2), 1.53 (m, 2H, CH_2), 1.02 (t, 3H, CH_3), ^{31}P NMR: –12.02. Anal. Calcd for $C_{16}H_{14}Br_2NO_4PS_2$ (539.20): C, 35.64; H, 2.61; N, 2.59. Found: C, 35.42; H, 2.58; N, 2.52 %.

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References

1 M.S. Bhatia and Pawanjit, *Experientia,* 1976, **32**, 1111.
2 R. Ismail, *Ger. Patent,* 1975, 1 543 539: *Chem. Abstr.,* 1975, **83**, 974 169.
3 S.D. Pastor and J.D. Spivack, *Phosphorus Sulfur*, 1983, **15**, 253.
4 J.D. Spivack, *Brit. Patent*, 1982, 1 087 399; *Chem. Abstr*, 1982, **97**, 198 374.
5 Z.B. Papanastassiou and T.J. Bardos, *J. Med. Chem.,* 1962, **5**, 1000.
6 C. Fest and K.J. Schmidt, *The Chemistry of Organophosphorus Pesticides*, Springer-Verlag, Berlin, 1982.
7 F. Dunning, B. Dunning Jr and W.E. Drake, *J. Am. Chem. Soc*., 1931, **53**, 3466.
8 L.C. Thomas and R.A. Chittenden, *J. Chem. Soc.*, 1961, 1913.
9 R.A. Nyquist, *Spectrochim. Acta,* 1963, **19**, 713.
10 L.C. Thomas, *The Interpretation of the Infrared Spectra of Organophosphorus Compounds*, Heydon, London, 1974.
11 P.M. Reddy, B.S. Reddy, and C.D. Reddy, *Heteroatom Chem.* 1996, **7**, 165.
12 C.D. Reddy, K.D. Berlin, R.S. Reddy, C.N. Raju, M.El-Masri and S. Subramanian, *Phosphorus, Sulfur Silicon,* 1993, **61**, 81.
13 M. Venugopal, B.S. Reddy, C.D. Reddy and K.D. Berlin, *J. Heterocyclic Chem.,* 2001, **38**, 275.
14 R.M. Silverstein and F.X. Webster, *Spectrometric Identification of Organic Compounds,* John Wiley & Sons, 6th edition, New York, 1998.
15 P.M. Reddy, B.S. Reddy, C.D. Reddy, and K.D. Berlin, *Indian J. Chem.,* 1995, **34B**, 1085.
16 G.M. Blackburn, J.C. Cohen and Lord Todd, *Tetrahedron Lett.* 1964, **39**, 2873.